International Journal of Clinical Pharmacy (2019) 41:42–48
https://doi.org/10.1007/s11096-018-0724-7

RESEARCH ARTICLE

Impact of hospital pharmacist interventions on the combination of citalopram or escitalopram with other QT-prolonging drugs

A. Chastang[1] · S. Renet[1,2] · J. Corny[1] · H. Beaussier[3] · A. Petre[1] · A. Lillo-Lelouet[4] · T. T. Phan Thi[1] · Y. Bézie[1]

Received: 2 February 2018 / Accepted: 5 September 2018 / Published online: 4 January 2019

Abstract

Background Citalopram and escitalopram can both induce dose-dependent QT prolongation. The risk of arrhythmia may be increased with concomitant use of other drugs that induce QT prolongation. *Objective* To evaluate the prevalence and impact of pharmacist interventions on the combination of citalopram or escitalopram with other drugs that induce QT prolongation. *Setting* A French hospital with 517 computerized beds. *Method* All cardiac adverse drug reactions (ADRs) related to citalopram or escitalopram reported to the French pharmacovigilance database (FPDB) were analyzed. Then, over a 6-month period, all computerized prescriptions including citalopram or escitalopram and drug–drug interactions (DDI) were analyzed by pharmacists using a computerized provider order entry system (DXCare®, Medasys). *Results* Only 27 cardiac ADRs related to citalopram or escitalopram were reported in the database. Among the 57,857 prescriptions and 2116 contraindicated DDIs (3.7 %) that were analyzed. 444 DDIs (0.8 %) were considered to be clinically relevant by pharmacists and physicians and 168 (i.e., approximately 30 %) were related to a combination including citalopram or escitalopram. Most of the prescriptions related to DDIs including citalopram or escitalopram were discontinued in response to a pharmacist intervention when initiated during the hospital stay. *Conclusion* A high number of hospital prescriptions including citalopram or escitalopram with another QT-prolonging drug occurred, highlighting the importance of involvement of clinical pharmacists in prevention of potential ADRs related to such contraindications.

Keywords Citalopram · Contraindicated drug–drug interactions · Drug safety · Pharmacist intervention · QT-prolonging drugs

Impacts on practice

- Practitioners should be aware that a high prevalence of combinations of citalopram and escitalopram with other drugs that induce QT prolongation can occur during hospitalization.
- Pharmacists must identify contraindicated drug-drug interactions and assess if they are clinically relevant.
- Spontaneous pharmacovigilance reporting by practitioners and pharmacists on the clinical effects of interactions possibly inducing QT prolongation would be useful for further studies.

Introduction

Adverse drug reactions (ADRs) are a major cause of morbidity and mortality, and a leading cause of hospital admissions [1, 2]. The exact number of ADRs is not

T.T. Phan Thi and Y. Bézie contributed equally to this work.

✉ Y. Bézie
ybezie@hps.fr

[1] Pharmacy Department, Groupe hospitalier Paris Saint-Joseph, 185 rue Raymond Losserand, 75014 Paris, France

[2] Clinical Pharmacy Department, University Paris Saclay, Paris, France

[3] Clinical Research Center, Groupe hospitalier Paris Saint-Joseph, 185 rue Raymond Losserand, 75014 Paris, France

[4] Centre Régional de PharmacoVigilance, Hôpital Européen Georges Pompidou, 20 Rue Leblanc, 75015 Paris, France

certain, and its determination is limited by methodological considerations. Nevertheless, ADRs represent a significant public health problem. In Europe, studies have estimated that ADRs cause approximately 197,000 deaths annually [3]. Moreover, they account for 5 % of all hospital admissions, and 5–10 % of hospitalized patients will experience an ADR during their hospital stay [3, 4]. However, the overall mortality rate attributable to ADRs is low, and it seems that most ADRs are preventable [5].

Among all reported ADRs, a list of 23 judged important for pharmacovigilance was proposed in 2009, including cardiac and vascular events such as acute myocardial infarction, QT prolongation, cardiac valve fibrosis, and venous thrombosis [6]. In this context, drugs that impair cardiac repolarization are particularly relevant as they may cause QT prolongation followed by ventricular arrhythmia and death. There is an extensive list of QT-prolonging drugs that can cause *torsades de pointes* (TdP). Many of these are commonly used in clinical practice, including antiarrhythmics, antimicrobials, antipsychotics, and antidepressants, with citalopram and escitalopram being two of the most commonly prescribed in Europe.

Citalopram and escitalopram can induce dose-dependent QT prolongation [7]. Although the effect in terms of QT prolongation appears to be greater for citalopram than escitalopram, the dose–QT correlation is similar for both drugs [8].

Although these two drugs are reasonably safe when used at therapeutic doses, the risk of arrhythmia may increase at high plasma levels [9] or when used concomitantly with other drugs that induce QT prolongation. Indeed, simultaneous use of more than one QT-prolonging drug or an association with another drug that alters their pharmacokinetic profile is an important risk factor for adverse outcomes [10].

Contraindicated drug–drug interactions (DDIs) are neglected by physicians and may cause ADRs and hospital admission. Contraindicated DDIs represent 3–5 % of all in-hospital drug errors [11]. Increased awareness by prescribers and involvement of a clinical pharmacist to minimize the risk of potentially harmful drug combinations are needed to overcome this problem. When identified, appropriate actions include recommendations for drug changes, dose clarification with the prescriber, correction of prescription errors, referral for further assessment, and recommendations for suitable nonprescription medication. However, pharmacist suggestions are not always followed by prescribers for many reasons, such as lack of time, poor therapeutic alternatives, or even lack of knowledge about the drugs.

Aim of the study

The objective of this study was to analyze all cardiac ADRs related to citalopram and escitalopram recorded in a French pharmacovigilance system, then evaluate the prevalence and impact of pharmacist interventions regarding their concomitant prescription with other drugs that induce QT prolongation.

Ethics approval

No informed consent was necessary, as the activity of the pharmacists was considered to be daily practice. The data collected were used in the study only and were anonymized.

Methods

Cases of cardiac ADRs related to citalopram or escitalopram reported to the French pharmacovigilance system

Spontaneous reports of cardiac ADRs related to citalopram or escitalopram were identified and analised in the French pharmacovigilance database (FPDB). All ADRs spontaneously reported by health professionals (and since 2011 by patients) to the network of pharmacovigilance centers are recorded in the database. Information about patients, ADRs, and drug exposure is available. These data may be used for regulatory decisions as well as in research and publications, being accessible to health professionals in collaboration with and agreement from the pharmacovigilance teams. The analysis of the FPDB in this study was conducted with the Centre Régional de Pharmacovigilance of the Hôpital Européen Georges Pompidou (Paris, France). In June 2014, the FPDB was searched for cases of any cardiac effect that named citalopram or escitalopram among the drugs responsible, whatever the mechanism, including DDIs [6]. The search was conducted from the start of use of citalopram in France (26 December 1994, the first marketing authorization of citalopram in France) until 30 June 2014.

DDIs involving citalopram or escitalopram in hospitalized patients

Data were collected over a 6-month period from May to December 2014 in a French hospital with 517 computerized beds (25 wards) using a computerized provider order entry system (DxCare®, Medasys, France). Clinical pharmacists routinely reviewed, 5 days per week, all computerized medical prescriptions involving citalopram or escitalopram.

The following parameters were studied: dosage, indications, and all DDIs. Drug review was mainly performed in the pharmacy department, or in the medical ward if necessary. DDIs were detected and extracted on a daily basis from the computerized prescription system (DxCare®) interfaced with the Vidal® database (drug monographs). The relevance of alert signals was then validated by the pharmacists. A DDI was defined as a drug pair contraindicated for concomitant use [12]. A major DDI was defined as an interaction which might be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects [13]. However, alerts for an association regarding a specific indication or dosage not specified in the prescription were considered irrelevant; in such situations, the pharmacist was not required to take further action. However, if the notification was relevant, the pharmacist had to alert the prescribing physician of the DDI.

Pharmacist interventions

Each intervention by a pharmacist was registered in a standardized document linked to the hospital's electronic medical record system. All variables were systematically registered in parallel in a Microsoft Excel database. The practitioner's decision after the pharmacist's intervention was also registered: measurement of QT intervals [electrocardiograms (ECGs)], discussion of the risk–benefit balance, discontinuation and replacement with an alternative drug with less or no potential to cause QT interval prolongation, or no further action (alert overridden).

Data analysis

Descriptive variables were analyzed in terms of percentage and standard deviation. Student's *t* test was performed for quantitative variables (i.e., discontinuation of medical orders related to an initial or renewed prescription). Variables with p-value <0.05 were regarded as statistically significant.

Results

Cases of cardiac ADRs involving citalopram or escitalopram reported to the French pharmacovigilance system

In this study, 458 cases of ADRs with citalopram or escitalopram as a suspected drug and 151 cases of ADRs with citalopram or escitalopram interacting with one (or more) drugs were extracted from the FPDB. Of these reports, only 27 (17.9 %) were cardiac ADRs (Table 1). Cardiac rhythm disorders, QT prolongation, and TdP were the main cardiac ADRs. Drugs associated with citalopram or escitalopram were mainly central nervous system drugs (benzodiazepine and antipsychotics) and sotalol. In contrast, our analysis did not find any common drugs known to cause TdP and contraindicated for concomitant use with citalopram or escitalopram (antiarrhythmics, macrolides, fluoroquinolones, antifungals, antiemetics, etc.) (Table 1).

DDIs involving citalopram or escitalopram in hospitalized patients

A total of 19,797 patients (55.4 % women) were analyzed, with mean hospital stay of 3.83 ± 4.92 days. Because some patients were hospitalized several times during the study period, the final analysis included 28,840 hospital stays. Mean patient age was 58.5 ± 20.5 years (Table 2). A total number of 57,857 prescriptions were analyzed; 2116 (3.7 %) contraindicated DDIs were detected by the computerized prescription system, among which 444 (21 %) were considered to be relevant by pharmacists. Specifically, 168 (37.8 %) of the relevant contraindicated DDIs involved citalopram or escitalopram (Table 3). Throughout the study, the time course evolution of DDIs involving citalopram or escitalopram was relatively stable, varying from one to three DDIs per day on average (Fig. 1). Among the torsadogenic drugs known to interact pharmacodynamically with citalopram or

Table 1 Distribution of cardiac adverse drug reactions (ADRs) involving citalopram or escitalopram

Cardiac ADR	Number (%) of cardiac ADRs	Other drugs mentioned in the report
Myocardial infarction	1 (3.7)	Atorvastatin
Heart failure	3 (11.1)	Hydroxyzine
Cardiac rhythm disorders	13 (48.1)	Oxazepam, clonazepam, quetiapine, zopiclone, sotalol, risperidone
QT prolongation and *torsades de pointes*	6 (22.2)	Risperidone, prazepam
Palpitations	2 (7.4)	Clonazepam, levomepromazine
Hypertension	1 (3.7)	
Cardiac valvulopathy	1 (3.7)	Benfluorex

Table 2 Patient characteristics

Characteristic	
Number of patients, *n*	19,797
Age, years[a]	58.5 ± 20.5
Women, %	55.4
Total number of drugs, *n*[b]	879,677

[a]Mean ± standard deviation

[b]This number is the sum of the different drugs prescribed during all hospital stays analyzed

Table 3 Prevalence of contraindicated DDIs involving citalopram or escitalopram

Interventions	
Number of prescriptions	57,857
Detected contraindications	2,116 (3.7)
Relevant contraindications	444 (21.0)
Including a combination with citalopram or escitalopram	168 (37.8)

Variables expressed as number (%)

escitalopram, antiarrythmic drugs were the most common, being involved 26 times (52 % of cases; Fig. 2). Indeed, amiodarone (20 times; 40 % of cases) and to a lesser extent sotalol (6 times; 12 % of cases) were implicated in more than half of the detected DDIs. Antipsychotic drugs (haloperidol, risperidone, and amisulpride) were the second most important class of drugs identified in the DDIs (16 times; 32 % of cases). Antiemetics (domperidone), known to cause TdP, were also associated with citalopram or escitalopram (four times; 8 % of cases). Finally, it is important to note that DDIs involving imidazole antifungals, antimalarials, and first-generation antihistamines with citalopram or escitalopram were not found throughout the study (Fig. 2).

Pharmacist interventions

The majority of interventions by pharmacists were carried out by telephone or computerized message (Table 4). Interestingly, we observed that 10 (62.5 %) prescriptions involving a DDI with citalopram or escitalopram were discontinued in response to pharmaceutical intervention when initiated during the hospital stay. In contrast, most of the practitioners did not follow pharmacist recommendations when the drugs were already prescribed at time of admission. Indeed, only 10 (19.4 %; $p < 0.01$) at-home treatment renewals were discontinued after intervention.

Discussion

The principal finding of this study is that a high number of hospital prescriptions with citalopram or escitalopram were associated with other QT-prolonging drugs. This result highlights the importance of the involvement of clinical pharmacists in prevention of potential ADRs related to drug interactions involving citalopram or escitalopram. Moreover, we noticed that, when a pharmacist detected an initial prescription containing the described contraindication, the prescriber usually agreed to modify the prescription, indicating the usefulness of pharmacist interventions in preventing prescription of contraindicated drugs.

It has been shown that patient safety can be improved through electronic prescribing, which decreases drug errors and ADRs [14–16]. Indeed, implementing a computerized physician order entry (CPOE) system decreases preventable ADRs; For instance, "pop-ups" alerts can be used when a documented allergy or interaction with another drug or health condition is detected. Nevertheless, practitioners often override these alerts. This behavior is partly related to loss of alertness, with prescribers being overloaded with alerts and clicking through them

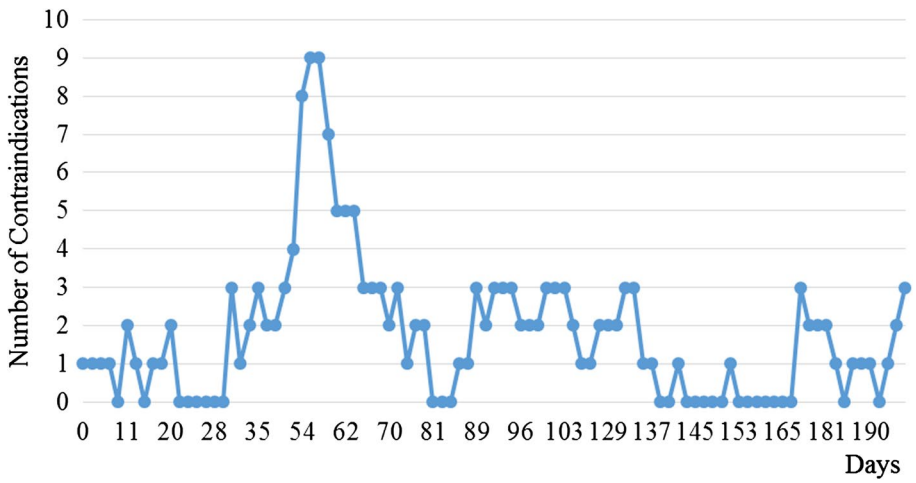

Fig. 1 Time course evolution of contraindicated drug associations involving citalopram or escitalopram among analyzed prescriptions

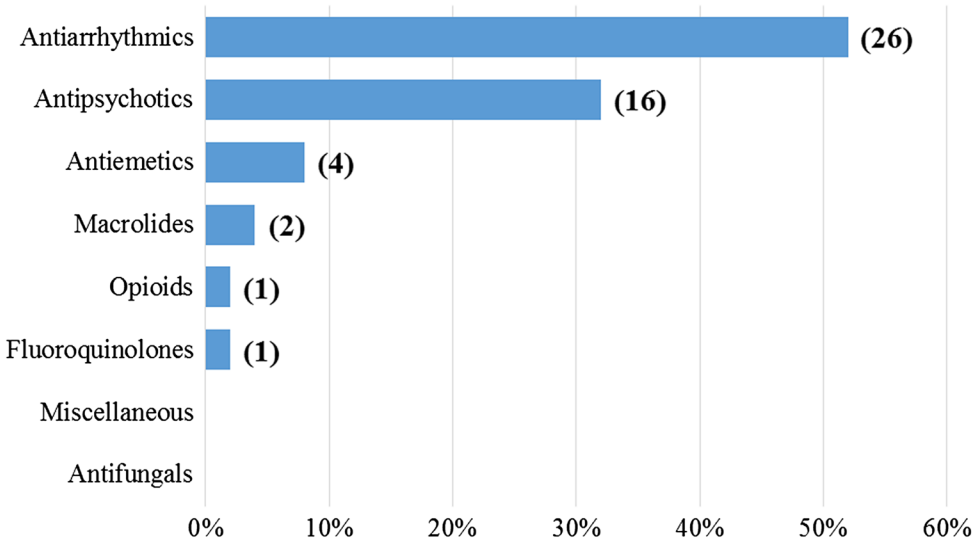

Fig. 2 Common drugs known to cause *torsades de pointes* in combination with citalopram and escitalopram, after prescription analysis. Numbers in parenthesis are the numbers of patient prescription profiles who had a combination of the therapeutic class or drug cited with citalopram/escitalopram. Antiarrhythmics: amiodarone (20), sotalol (6); antipsychotics: haloperidol (4), cyamemazine (5), amisulpride (4), chlorpromazine (2), tiapride (1); antiemetics: droperidol (4); macrolides: rovamycin (2); opioids: methadone (1); fluoroquinolones: levofloxacin (1)

Table 4 Outcome of pharmacist interventions related to citalopram or escitalopram contraindications

	n (%)
Pharmacist interventions	
Direct contact with prescriber	41 (82)
Computerized message	5 (10)
Both	4 (8)
Consequence of pharmacist interventions	16
Initial prescription discontinued	10 (62.5)
At-home treatment renewal discontinued	6 (19.4)*
ECG monitoring	34 (68)

Variables expressed as number (%). *$p < 0.01$ versus initial prescription discontinued

rather than reading each one. This situation may cause prescription errors related to nondetection of important drug interactions [17]. The lack of specificity of these alerts probably worsens this phenomenon [18], as they mainly highlight nonserious interactions [19]. Our study showed that, among the 3.7 % (2116/57,857) of the analyzed prescriptions with a contraindication, only 21 % (444/2116) were considered to be clinically relevant by pharmacists, in good agreement with our previous observations on this topic. We observed that practitioners have difficulties in translating drug contraindications into clinical practice. During our study, the daily number of relevant drug contraindications associated with citalopram or escitalopram remained constant, justifying pharmacist interventions. These interventions were mostly taken into account when the DDI was initiated during the hospital stay, demonstrating that these contraindications are often avoidable. Nevertheless, prescribers tended to maintain prescriptions initiated before hospitalization. This behavior can be explained by various obstacles, such as reluctance to change long-term treatment, lack of communication with primary-care practitioners, or lack of knowledge about drugs [20].

Of all the contraindications reported to our CPOE system, citalopram and escitalopram combined with other torsadogenic drugs appeared to be the main cause of alerts detected by pharmacists. QT prolongation is a serious ADR because it can lead to sudden cardiac death [21]. The QT prolongation effect of citalopram or escitalopram has long been described in many case reports, with cardiac toxicity revealed in cases of high doses [9–22]. Drug dosage is only one of several factors that increase the risk of QT interval prolongation. Other risk factors include advanced age, existing cardiac illness, multiple medical illnesses, electrolyte disturbances (hypokalemia, hypomagnesemia), and concomitant use of other QT-prolonging drugs. These factors would be particularly important for citalopram and escitalopram, which prolong the QT interval marginally [8].

Escitalopram, the *S*(+)-enantiomer of racemic citalopram that was developed to reduce the cardiac toxicity of citalopram, is still not the safest alternative among this drug class, based on cardiac risk factors. Other selective serotonin reuptake inhibitors should be chosen as an alternative, based on individual risk factors for arrhythmia [23].

There is an extensive list of drugs that can prolong the QT interval. Moreover, the problem of acquired QT prolongation is further complicated in patients taking multiple drugs. Indeed, there is a relatively high risk that a patient will receive at least two drugs whose interaction will result in QT interval prolongation [24]. These interactions lead to alterations in drug metabolism or pharmacokinetics. These drugs include antiarrhythmics, antihistamines, gastrointestinal prokinetic agents, antiemetics, antipsychotic drugs, and agents used in drug dependence therapy [24, 25].

We demonstrated that antiarrhythmics (mainly amiodarone and sotalol) and some antipsychotics were the most common drugs involved in contraindicated DDIs with citalopram or escitalopram in our hospital. These results are not in agreement with the analysis of the FPDB, where no cases of cardiac ADRs with citalopram and escitalopram were related to such drug associations. A multicenter study might confirm these results. However, our results raise several questions: Are these drug associations with citalopram and escitalopram underreported, are they underdiagnosed, or are they clinically irrelevant?

Underreporting of ADRs is well known and inherent to the pharmacovigilance system [26, 27]. Reasons suggested for this include lack of knowledge or awareness about pharmacovigilance programs, inadequate risk perception, insufficient training to identify ADRs, carelessness, or fear of litigation by patients or colleagues [28].

The absence of management (alternative pharmacotherapy) to avoid contraindicated DDIs strongly suggests that clinicians are not aware of this risk. In the absence of cases reported to the French pharmacovigilance system, substantial effort has to be made to diagnose and report any cardiac ADRs related to this potential drug interaction. This also strongly supports communication to prescribers, as this drug contraindication is probably more prevalent than they might think.

Our final point relates to the clinical relevance of these contraindicated DDIs. Indeed, many patients may be taking concomitant drugs that prolong the QT interval, including citalopram and escitalopram. No fatal cardiac ADRs have been reported in this context to the French pharmacovigilance system. Furthermore, the designation "contraindication" could appear slightly excessive, given that some regulatory agencies (e.g., in Canada) have proposed a "precaution to use" instead. Nevertheless, the risk of TdP increases significantly with concurrent use of more than one QT-prolonging drug, or concomitant use of drugs that alter liver metabolism [29]. Although indiscriminate combinations of QT-prolonging drugs do not necessarily result in additive QT prolongation, the increased risk of concomitant use of citalopram or escitalopram with other drugs known to present this risk is well established [30]. Moreover, because sudden cardiac death is rare and its causes are difficult to identify clearly, we do not believe that studies and pharmacovigilance databases can provide sufficient information to overcome this contraindication at the present time. We encourage everyone (practitioners, pharmacists, drug manufacturers, and regulatory agencies) to periodically publish full case reports of psychotropic drug-induced QT interval prolongation, TdP, and sudden cardiac death, to improve understanding of the clinical implications of prescribing such drugs.

The main limitation of this study is that electrocardiograms of patients who continued to receive contraindicated drugs after physicians rejected pharmacist interventions were not analyzed. Thus, we cannot report on whether these patients had sustained QT prolongation. A multicenter study might be able to confirm these results.

Conclusions

This study shows a high prevalence of contraindicated DDIs involving citalopram and escitalopram in hospitalized patients, although no clinical manifestations were observed. The role of clinical pharmacists is important for identification and prevention of such DDIs. Pharmacovigilance data based on spontaneous reports do not support the clinical consequences of contraindicated DDIs involving citalopram and escitalopram. Therefore, these results call into question the clinical significance of such drug–drug contraindications and demonstrate that more studies are needed to establish clear recommendations.

Acknowledgements None.

Conflicts of interest The authors declare no conflicts of interest.

Funding None to declare.

References

1. Sultana J, Cutroneo P, Trifiro G. Clinical and economic burden of adverse drug reactions. J Pharmacol Pharmacother. 2013;4(Suppl 1):S73–7.
2. Sikdar KC, Dowden J, Alaghehbandan R, MacDonald D, Peter P, et al. Adverse drug reactions in elderly hospitalized patients: a 12-year population-based retrospective cohort study. Ann Pharmacother. 2012;46(7–8):960–71.
3. Tache SV, Sonnichsen A, Ashcroft DM. Prevalence of adverse drug events in ambulatory care: a systematic review. Ann Pharmacother. 2011;45(7–8):977–89.
4. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug Saf. 2015;38(5):437–53.
5. Lazarou J, Pomeranz B, Corey P. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;79:1200–5.
6. Trifiro G, Pariente A, Coloma PM, Kors JA, Polimeni G, et al. Data mining on electronic health record databases for signal detection in pharmacovigilance: which events to monitor? Pharmacoepidemiol Drug Saf. 2009;18(12):1176–84.
7. Lam R. Antidepressants and QTc prolongation. J Psychiatry Neurosci. 2013;38(2):E5–6.
8. Hasnain M, Howland RH, Vieweg WV. Escitalopram and QTc prolongation. J Psychiatry Neurosci. 2013;38(4):E11.

9. Álvarez E, Vieira S, Garcia-Moll X. Citalopram, escitalopram and prolonged QT: warning or alarm? Rev Psiquiatr Salud Ment. 2014;7(3):147–50.
10. Coughtrie A, Behr E, Layton D, Marshall V, Camm AJ, et al. Drugs and life-threatening ventricular arrhythmia risk: results from the DARE study cohort. BMJ Open. 2017;7(10):e016627.
11. Leape LL, Bates DW, Cullen DJ, Cooper J, Demonaco HJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA. 1995;274(1):35–43.
12. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. Drug Saf. 2007;30(10):911–8.
13. Barrons R. Evaluation of personal digital assistant software for drug interactions. Am J Health Syst Pharm. 2004;61(4):380–5.
14. Kannry J. Effect of e-prescribing systems on patient safety. Mt Sinai J Med. 2011;78(6):827–33.
15. Kaushal R, Kern LM, Barron Y, Quaresimo J, Abramson EL. Electronic prescribing improves medication safety in community-based office practices. J Gen Intern Med. 2010;25(6):530–6.
16. Nuckols TK, Smith-Spangler C, Morton SC, Asch SM, Patel VM, et al. The effectiveness of computerized order entry at reducing preventable adverse drug events and medication errors in hospital settings: a systematic review and meta-analysis. Syst Rev. 2014;3:56.
17. Footracer KG. Alert fatigue in electronic health records. JAAPA. 2015;28(7):41–2.
18. Bates DW, Leape LL, Cullen DJ, Laird N, Petersen LA, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA. 1998;280(15):1311–6.
19. Bobb A, Gleason K, Husch M, Feinglass J, Yarnold PR, et al. The epidemiology of prescribing errors: the potential impact of computerized prescriber order entry. Arch Intern Med. 2004;164(7):785–92.
20. Anthierens S, Tansens A, Petrovic M, Christiaens T. Qualitative insights into general practitioners views on polypharmacy. BMC Fam Pract. 2010;11:65.
21. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003;89(11):1363–72.
22. Tampi RR, Balderas M, Carter KV, Tampi DJ, Moca M, et al. Citalopram, QTc prolongation, and torsades de pointes. Psychosomatics. 2015;56(1):36–43.
23. Funk KA, Bostwick JR. A comparison of the risk of QT prolongation among SSRIs. Ann Pharmacother. 2013;47(10):1330–41.
24. Wisniowska B, Tylutki Z, Wyszogrodzka G, Polak S. Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect—comprehensive overview of clinical trials. BMC Pharmacol Toxicol. 2016;17:12.
25. Li M, Ramos LG. Drug-induced QT prolongation and torsades de pointes. P T. 2017;42(7):473–7.
26. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385–96.
27. Pushkin R, Frassetto L, Tsourounis C, Segal ES, Kim S. Improving the reporting of adverse drug reactions in the hospital setting. Postgrad Med. 2010;122(6):154–64.
28. Khan SA, Goyal C, Chandel N, Rafi M. Knowledge, attitudes, and practice of doctors to adverse drug reaction reporting in a teaching hospital in India: an observational study. J Nat Sci Biol Med. 2013;4(1):191–6.
29. Allen LaPointe NM, Curtis LH, Chan KA, Kramer JM, Lafata JE, et al. Frequency of high-risk use of QT-prolonging medications. Pharmacoepidemiol Drug Saf. 2006;15(6):361–8.
30. Meid AD, Bighelli I, Machler S, Mikus G, Carra G, et al. Combinations of QTc-prolonging drugs: towards disentangling pharmacokinetic and pharmacodynamic effects in their potentially additive nature. Ther Adv Psychopharmacol. 2017;7(12):251–64.